REMARKS

Claims 1-53 and 56-60 are currently pending in the application. Claims 20-26 and 45-51 have previously been withdrawn from consideration due to a previous election of species. By this amendment, claims 54 and 55 are cancelled (having previously been withdrawn from consideration due to a restriction requirement); the specification is amended; and new claims 57-60 are added for the Examiner's consideration. The foregoing separate sheets marked as "Listing of Claims" shows all the claims in the application, with an indication of the current status of each.

Claim Rejections

35 USC § 103(a)

Claims 1-19, 27-44, and 56 stand rejected under 35 USC § 103(a) as obvious over Shively et al. (U.S. patent 5,407,683, hereafter "Shively") in view of Benet et al. (U.S. patent 5,716,928, hereafter "Benet") and Yau (U.S. patent 5,541,287, hereafter "Yau"). This rejection is traversed.

The present invention provides compositions comprising a structured fluid and a compound present in the structured fluid, the compound being less than 5% by weight soluble in soybean oil. The structured fluid comprises three elements: 1) a polar solvent; 2) a lipid or surfactant; and 3) an essential oil or dissolution/solubilization agent or both. For purposes of examination, water has been selected as the polar solvent; pluronic has been selected as the lipid or surfactant; spearmint oil has been selected as the essential oil, and gentisic acid has been selected as the dissolution/solubilization agent. Applicant asserts that no combination of the references cited by the Examiner renders the present invention obvious.

Shively provides compositions of matter that include pharmaceutically effective amounts of taxol solubilized in a pharmaceutically acceptable carrier comprising an oil (column 4, lines 41-44). The oils employed by Shively are described as "having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes" and "preferably between about 1.6 and about 1.7 Debyes" (see abstract; column 3, lines 57-60; and column 4, lines 44-47). They are further described as "known in the art" and include "vegetable, flower, animal and marine oils" (column 4, lines 67-68). The preferred embodiments of the invention utilize oils from deep water

mammals, preferably oils having ether lipid as a major component, especially orange roughy or shark liver oil, squalene, or squalene (column 5, lines 1-5). According to Shively, pharmaceutically effective emulsions are formed from a mixture of taxol, oil and an aqueous phase such as water.

Examiner's comments regarding the application of this reference to the rejection of the claims of the present application are very brief. Examiner does not state precisely which elements of the composition taught by Shively have been equated with the components of the composition of the present invention. Because, according to the Examiner, the other two cited references (Benet and Yau) supply essential oils and gentisic acid, respectively, Applicant assumes that Examiner is relying on Shively to provide the remaining components of the composition of the present invention, namely 1) water and 2) pluronic. Logically, pluronic must be equated with the oil described by Shively. However, Applicant notes that the oil used in the composition of Shiveley must possess a dipole moment of "between about 0.5 Debyes and about 2.0 Debyes" and "preferably between about 1.6 and about 1.7 Debyes". Pluronic (e.g. Pluronic L-122) does not fit this description. Indeed, in a paper by the highly respected polymer scientist J. P. Flory, together with J. E. Mark (J.E. Mark and J. P Flory, *J. Am. Chem. Soc.*, vol. 88 (1966), p. 3702, copy enclosed) both experimental and theoretical evidence show that the root-mean-square dipole moment of the polyoxyethylene portion of the Pluronic molecule is given by the formula:

$$\mu_{RMS} = \sqrt{0.58} \times 0.81\mathbf{D} \times \sqrt{\mathbf{n}}$$

where 0.58 is the so-called dipole moment ratio, 0.81Debyes is the RMS average bond dipole moment (averaged between the O-C, C-C, and C-O bonds of the polyoxyethylene monomer unit), and n is the number of bonds in the PEO chain, which in the case of L-122 is on the order of 30-40, on average. This number thus works out to be approximately 3.7 Debye units, and this is the contribution from just one of the blocks, so that the dipole moment of the entire L-122 molecule is significantly higher than this, in fact on the order of 10, much higher than the 0.5-2 D cited in the Shiveley patent. This underscores the fundamental distinction between the Pluronics of the present application, which are surfactants (which contain highly polar groups operative as head groups, and thus possess high dipole moments), and the marine oils of Shiveley, which are

not.

Thus, Shively is not a suitable primary reference for combination with other references for use in an obviousness rejection of the claims of the present application since it does not supply the elements for which it is relied on by the Examiner. In addition, Shively does not supply any motivation whatsoever for the addition of other compounds to the compositions disclosed therein. In particular, Shively does not show or suggest the possibility or advisability of including essential oils and/or dissolution/solubilization agents (e.g. spearmint oil, gentisic acid) in the compositions. Shively is perfectly content with the level of solubility of taxol that is achieved in the compositions disclosed therein without adding any other ingredients.

New claim 57 recites that the structured fluid of claim 1 is a liquid crystalline phase, an L1 phase, an L2 phase, an L3 phase, or a combination thereof. The subject matter of new claim 57 is clearly distinguished from the subject matter of Shively, which teaches only emulsions.

Nevertheless, Examiner cites Benet as one of two references to "combine" with Shively. The Examiner states that Benet supplies the teaching of "essential oils to increase the bioavailability of pharmaceutical compounds", and that spearmint oil and taxol are "disclosed". Applicant submits that Examiner's assessment of Benet is highly superficial. In fact, what Benet teaches is simply the co-administration of oral pharmaceuticals and essential oils (column 2, lines 33-43; column 3, lines 21-29). The co-ingestion of an essential oil has the effect of increasing the bioavailability of the pharmaceutical, the effect being attributed to the inhibition by the essential oil of enzymes of the cytochrome P450 3A class in the gut (column 2, lines 9-20). "Co-administration" is defined by Benet to include "concurrent administration (administration of the essential oil and the drug at the same time) and time-varied administration (administration of the essential oil at a time different from that of the drug), as long as both the essential oil and the drug are present in the gut lumen and/or membranes during at least partially overlapping times." (column 25, lines 16-22). Thus, according to the teachings of Benet, *the essential oil does not even have to be administered at the same time, and thus not even in the same composition, as the pharmaceutical*, in order to be effective. This is because the essential oil taught by Benet is not an integral component of the composition that contains the drug, and is not described as bearing any special relationship to the drug itself. Rather, the essential oil works by inhibiting enzymes in

the gut. Benet teaches that a recipient of a pharmaceutical can simply ingest the pharmaceutical and an essential oil at roughly the same time in order to achieve the beneficial effects of the essential oil.

The co-administration of essential oils as taught by Benet has nothing to do with the *incorporation* of an active pharmaceutical compound (e.g. taxol) *in* an essential oil (e.g. spearmint)-rich structured fluid where the essential oil is by design, and by necessity, in direct contact with the active in the formulation, as is the case in the present invention. There is nothing in Benet that teaches or suggests solubilization of an active within a structured fluid that contains an essential oil. Applicant notes that the only appearances of the terminology or concepts of "solubilization" and "dissolution" in Benet are in connection with the dissolution of the essential oil *itself* for purposes of applying the oil to a cell culture test (column 28 lines 22-23; column 29 lines 61-65; and column 30 lines 6-8), the classification of drugs as to the relative solubilities in octanol or water (column 16 lines 38-41), or the dissolution of a formulation in the body after ingestion (column 26 lines 52-59).

Further, Benet offers no motivation for combining the technology presented therein with any other methods, such as those discussed by Shively, and does not show or suggest any advantages of the co-administered drug being particularly dissolved in an oil with a dipole moment of between about 0.5 Debyes and about 2.0 Debyes as taught by Shively, much less with the further addition of gentisic acid as taught by Yau (see the following discussion of Yau).

The Examiner further cites Yau, briefly describing that reference as teaching "Gentisic acid as a radio protectant" and briefly stating that "Taxol is disclosed". Again, the Examiner's assessment of this reference is highly superficial. In fact, Yau teaches radiolabeled small molecules for use in diagnostic or therapeutic pretargeting methods. Pretargeting is described in column 3 at lines 41-49 as involving target site localization of a targeting moiety that is conjugated with one member of a ligand/antiligand pair. After a time period sufficient for optimal target-to-non-target accumulation of this targeting moiety conjugate, active agent conjugated to the opposite member of the ligand/antiligand pair is administered and is bound to the targeting moiety conjugate at the target site. Thus, the method provides a way of bringing the active agent into close proximity with the target and prevents accumulation of active agent at non-target areas. The target may be, for example, a tumor, and the active agent may be an anti-

tumor agent. The thrust of the invention is to provide novel radioiodinated biotin derivatives that are of relatively low molecular weight, in contrast to prior art radioiodinated biotin derivatives that are of relatively high molecular weight (column 6, lines 33-38, and see the claims which depict structures of the derivatives). The Examiner states that "Taxol is disclosed" and refers to column 9, line 28. Howwever, taxol appears at that location only in a "laundry list" of many possible active agents that can be conjugated to the biotin derivatives and delivered by the methods of the invention. Taxol is not described by Yau as provided in a composition in which it is dissolved, and certainly not in a structured fluid as is the case in the present invention.

The Examiner states that gentisic acid is used as a radioprotectant in the practice of the invention of Yau. This is correct in that at column 29, at lines 29-30, gentisic acid is listed in a list of possible antioxidants that can be used to protect and stabilize the radiologically sensitive macrocyclic ring of the low-molecular weight biotin derivatives, with ascorbic acid being the preferred radioprotectant. Gentisic acid is neither shown nor suggested as relevant to the solubilization of taxol (or any other substance) in any way, as is the case in the present invention. Gentisic acid is not shown or suggested as a component of a structured fluid of any type, as is the case in the present invention. Yau is silent as to the use of structured fluids for the solubilization of drugs. Gentisic acid is taught only as a radioprotectant.

In point of fact, Yau teaches the chemical modification of drugs by conjugation to a targeted biotin derivative in order to improve their performance. This approach, in fact, teaches away from the present invention, since the latter is entirely focused on the solubilization of drugs in their existing form, without chemical modifications that can greatly prolong the process of approval and acceptance of a drug. When a given drug is not performing well, it is well recognized in the art that two diametrically opposed approaches can be attempted to remediate the situation: one being chemical modification of the drug, and the other being improved solubilization of the existing drug, which obviates chemical modification. From a legal perspective, the chemical modification of a drug changes it to a New Chemical Entity (NCE), and introduces new regulatory hurdles for the compound. The approach of Yau introduces NCEs, whereas that of the present invention does not. Indeed, if the invention of Yau were applied to paclitaxel, the final drug formulation *would not have paclitaxel per se as an ingredient*, in solubilized or any other form

Neither Shively nor Benet (or a hypothetical combination of the two) involves the use of radiation, or refers to the need for radioprotection of the components of any compositions described therein. There would therefore be no motivation to combine gentisic acid as taught by Yau with the compositions taught by Shively and Benet. Shively and Benet do not employ compounds with radiosensitive macrocyclic rings. A combination of Yau with Shively and Benet must result in a peculiar mixture of a drug (e.g. taxol) conjugated to a low molecular weight biotin derivative with enough radioprotectant to protect the biotin derivative, plus a drug (e.g. taxol) dissolved in an oil with a dipole moment of between about 0.5 Debyes and about 2.0 Debyes, somehow formulated to permit oral co-administration with an essential oil, although the essential oil need not be co-administered at the same time. This combination is obviously non-sensical.

In contrast, the present invention provides a precisely defined composition in which there is a compound that is present *in* a structured fluid, one component of which is an essential oil. The invention is based on the surprising discovery that essential oils such as spearmint oil, in combination with other components of the structured fluid, provide superior *solubilization* systems for pharmaceutical agents and can form structured fluids that are pharmaceutically acceptable for administration. The existence of art describing other important uses of essential oils does not render obvious the direct incorporation of essential oils into complex structured fluids, and in particular the finding that the resulting structured fluids display a synergistic combination of properties that make them superior for the solubilization and delivery of drugs. Similarly, teachings of important uses of gentisic acid—of which there no doubt are many—does not render obvious the use of gentisic acid as described in the present invention. The use of gentisic acid in the present invention results in a synergistic combination of a sufficiently high partition coefficient (making it bilayer-associated) and strongly polar groups, such that the compound not only strongly improves the polar characteristics of the surfactant bilayer in the structured fluids of focus, but also can be used to modulate the phase behavior of the surfactant system to achieve a desired liquid or liquid crystalline phase; the compound is, furthermore, FDA-accepted for use in injectable formulations. Nothing in Shively, Benet or Yau or in any combination of these three references anticipates the features and functionalities of the structured fluid of the present invention.

New claim 58 recites that with regard to the composition of claim 1, the compound that is present in the structured fluid is dissolved in the structured fluid. The subject matter of new claim 58 is clearly distinguished from the work of Benet, which does not teach dissolution of the a compound in a structured fluid.

An invention is not a mere collection of parts. In particular, the present invention is not a mere collection of substances each of which has some beneficial attribute that is displayed in the collection, independent of the presence of the other substances in the mixture. On the contrary, the present invention is directed to the surprising finding that the components listed in claim 1, when combined according to the teachings set forth in the specification, form a structured fluid into which substances that are otherwise difficult to dissolve can be incorporated and retained for administration.

In view of the foregoing, Applicant requests reconsideration and allowance of claims 1-53 and 56-60 of the application.

New Claims 59 and 60

New claims 59 and 60 depend from claim 1 and recite that the essential oil or dissolution/solubilization agent of claim 1 is: 1) an essential oil (claim 59); or, 2) a dissolution/solubilization agent (claim 60). Since both of these types of compounds are recited in original claim 1, and claims 59 and 60 recite only one or the other, Applicant submits that the new claims do not add any new matter.

Applicant respectfully requests examination and allowance of new claims 59 and 60.

Other matters

In the specification, the Examples Section has been replaced by a replacement Examples Section in which Example 8 has been deleted, and subsequent examples have been renumbered to preserve the consecutive numbering of the examples. Upon review of the application after filing, Applicant noted that examples 4 and 8 describe identical experimental results. Thus, to eliminate redundancy, example 8 has hereby been deleted.

Applicant submits that this amendment does not constitute the introduction of new matter, the amendment serving only to remove redundant material from the application.

Conclusion

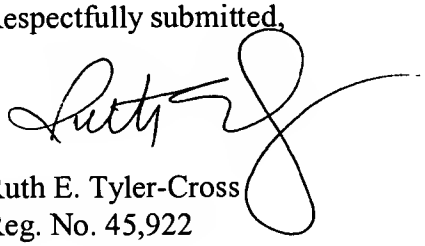
In view of the foregoing, it is requested that the application be reconsidered, that claims

1-19, 27-44, and 56 -60 be allowed, and that the application be passed to issue. Since generic claims 1 and 27 are allowable, withdrawn claims 20-26 and 45-51 should also be allowed.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



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